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Chapter 3

Chronic Inducible Urticaria Part I

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http://dx.doi.org/10.5772/68069

Abstract

Urticaria is a common mast cell-driven disease which is characterized by red, itchy swellings. Urticaria, that persists more than 6 weeks in a repetitive manner (each lesion disappearing in <24 h), is called chronic urticaria. Chronic urticaria can be either spontaneous without the need of a trigger, or inducible in which with a known trigger the lesions can be provoked. Chronic inducible urticarias include the physical urticarias and some other forms such as cholinergic urticaria.

Keywords: urticaria, chronic urticaria, inducible urticaria, cholinergic urticaria, contact urticaria

1. Introduction

Urticaria, also known as hives, is a common, mast cell-driven, itchy condition which is characterized by red/pink, swollen whealing of the skin [1]. The lesions can vary from a few millimeters to tens of centimeters. Chronic urticaria is defined when the transient lesions that disappear in <24 h and last more than 6 weeks in repetitive manner [2]. Most of the chronic urticaria cases are idiopathic [3]. Chronic spontaneous urticaria is the spontaneous appearance of wheals, angioedema or both due to known or unknown causes for a period longer than 6 weeks. In case of a known trigger that causes whealing, angioedema or both at every exposure, chronic inducible urticaria term is used. Chronic inducible urticarias consist of physical urticarias (PUs) and cholinergic urticaria (CU) [1, 3, 4]. **Figure 1** demonstrates the classification of urticaria according to EAACI/GA²LEN/WAO 2013 guideline.

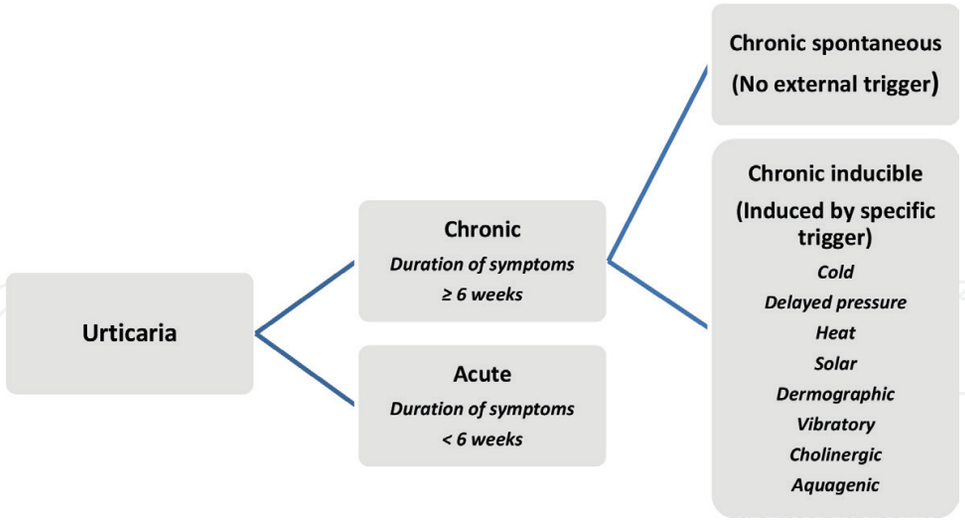

Figure 1. Classification of urticaria, according to EAACI/GA2LEN/WAO 2013 guideline.

Physical urticaria (PU) is a subgroup of acquired, chronic inducible urticaria which is associated with a known physical trigger [5]. In PU, the symptoms are induced by exogenous physical triggers such as friction, pressure, vibration, cold, heat or solar radiation. All the PUs may manifest with both wheals and angioedema at the sites of the triggers with the exceptions that urticaria factitia (symptomatic dermographism) presents with wheals only and pressure urticaria presents with angioedema only [6, 7]. **Table 1** summarizes the types and subtypes of chronic inducible urticaria and the triggering agents.

Cholinergic urticaria is another subtype of inducible urticaria. Because of the fact that the symptoms are not triggered by exogenous physical exposure, cholinergic urticaria is not considered as PU. Rather, it is induced by an increase in the body core temperature [8].

Almost 0.5% of the population suffers from chronic inducible urticaria that makes nearly 15–25% of all chronic urticarias [7]. All forms of urticaria do not only cause impaired quality of

Type	Subtypes	Trigger
Physical urticarias	Cold urticaria	Cold contact (air, water and solid)
	Delayed pressure urticaria	Vertical pressure
	Heat urticaria	Hot contact (air, water and solid)
	Solar urticaria	UV or visible light
	Symptomatic dermographism	Mechanical stroking
	Vibratory urticaria	Vibration
Other inducible urticarias	Aquagenic urticaria	Water at any temperature
	Contact urticaria	(Non)immunological contactant
	Cholinergic urticaria	Increment of body temperature
	Exercise-induced anaphylaxis	Physical exercise

Table 1. Classification of chronic inducible urticaria.

http://dx.doi.org/10.5772/68069

life but also affect performance at social life, school and work [9]. PU is classified depending on the type of the physical trigger. They are diagnosed by using different provocation tests inducing wheals and sometimes angioedema [3]. It is important to make provocation tests after taking the patient's history in order to get a proper diagnosis. One must be very careful during the provocation tests as systemic symptoms including shock can develop along the course [10]. In chronic inducible urticaria, the threshold of the causative trigger must be established to assess the severity of the condition. These threshold levels also allow us to evaluate the activity of the diseases and the response to the therapy [11]. PU generally accompanies other forms of chronic urticaria such as spontaneous urticaria and/or other inducible urticaria types. Therefore, every patient with one of the PUs must be tested with all physical triggers that seem to be relevant from the medical history [12]. The result of the provocation test changes according to the medical status of the patient. That's why the test should be done prior to the treatment if possible. Testing should be performed on skin areas which have not been complicated with wheals recently. Because affected skin areas exhibit a refractory period after urticarial reactions. In case of a negative result despite a strong suspicion, the testing can be repeated several times. In cholinergic urticaria, the patient must be asymptomatic for 48 h before testing [6].

2. Cholinergic urticaria (CU)

Cholinergic urticaria, simply, is a type of chronic urticaria which is triggered by elevated body temperature. Physical exercise, strong emotions, hot or spicy food and hot showers seem to be the most common causes [13]. CU accounts for 5% of all chronic urticaria cases [7]. Generalized flushing, itching and wheals surrounded by macular erythema make the clinical picture in CU. The lesions spread from the trunk and neck to the extremities. Some of the CU cases are complicated with systemic symptoms such as hypotension, angioedema and bronchospasm [14]. CU due to exercise starts 5–10 min after the beginning of the exercise and maximizes after 12–25 min [15].

The pathophysiology in CU is thought to be related to the elevation of histamine in the serum. Adachi et al. proposed that CU occurs after a type 1 allergic reaction to the patient's own sweat. They reported that the patients underwent autologous sweat testing and demonstrated an immediate skin reaction [8].

In case of a suspicion, confirmatory testing should be conducted. Appearance of whealing after the intradermal injection of 0.01 mg methacholine in 0.1 ml saline is diagnostic. Assuming that only one-third of the patients demonstrate positive testing CU cannot be ruled out with a negative provocation test [9]. Specific provocative challenges such as exercise, hot showers or spicy food trials can also be tried. The best way to provoke is to increase the individual's body temperature by submerging the patient in a hot water bath at 40°C. Developing of generalized hives confirms the diagnosis [6]. Unfortunately, this testing can have interference with aquagenic urticaria (AU) or heat urticaria.

Best treatment of CU is the avoidance of the offending stimulus in cases where possible. First-line medical therapy is the oral antihistamines. Hydroxyzine is believed to be more effective than the others [16]. Oral anticholinergics have been tried with failure mostly. Use of

pre-exercise propranolol 80 mg daily has been found effective in controlling the symptoms of CU [17]. These data have not been supported by further studies because of the fact that beta-blockers, themselves, cause allergic reactions.

The prognosis of CU is mostly pleasing. About 70% of the patients heal within 10 years of the diagnosis. Sibbald et al. estimated the duration of CU to be 3–16 years with an average of 7.5 years [2].

Cholinergic urticaria must be distinguished from exercise-induced anaphylaxis (EIA). The main symptoms of EIA include laryngospasm, bronchospasm, vascular collapse, fatique, vocal changes, gastrointestinal upset, flushing and hives [18]. In contrast to CU, the urticarial plaques are larger, up to 10–15 mm. All types of exercise including walking can be the trigger. In EIA, although the anaphylaxis symptoms are at the forefront, only a few cases of death have been reported [19].

EIA is treated like any other forms of anaphylaxis. Epinephrine is the life-saving treatment. Diphenhydramine 25–50 mg is helpful. Systemic steroids are used to prevent delayed biphasic reactions [20]. Any individual with the diagnosis of EIA should carry an epinephrine autoinjector [21]. Cetirizine and montelukast combination also has been reported to be useful in preventing symptoms of EIA [22].

CU can be differentiated from EIA with the size of the whealings. Also, in CU, the hives are in the front, whereas the edema and the anaphylaxis are in the front in case of EIA. In addition, passive warming test in a bath and methacholine injection tests are positive in CU [23].

3. Aquagenic urticaria (AU)

Aquagenic urticaria (AU) is a rare form PU which is characterized by wheals following cutaneous exposure to water, including tears and sweat. Mostly, 1–3 mm follicular wheals and 1–3 cm erythematous flares surrounding them are present. The lesions develop 20–30 min after exposure to water. Lesions usually resolve in 30–60 min after the cessation of contact to water [4]. Most of the patients are peri-pubertal females. Trunk and proximal arms are the most commonly affected sites, sparing palms and soles [5]. Wheezing and dyspnea can accompany the lesions. When there is such a systemic symptom, large lesions rather than 1–3 mm punctate lesions are present [24].

Most of the AU cases are sporadic. However, there are some reports of familial cases. No specific gene locus has been identified so far [5]. There are few cases showing the association of AU and HIV infection and papillary thyroid gland carcinoma [25, 26].

The pathogenesis of AU is not clear yet. In 1981, Tkach hypothesized that sudden changes in osmotic pressure around hair follicles, leading to passive diffusion of water caused whealing [27]. A recent proposal involves existence of water-soluble antigens in the epidermis which later migrate to dermis and cause histamine release [10]. The lack of a proper etiologic mechanism makes AU difficult to treat.

http://dx.doi.org/10.5772/68069

Water challenge test is necessary for the proper diagnosis. For this, water at room temperature is applied to a cloth, and this cloth is applied to patient's skin for 20 min. In case of an urticarial lesion, the provocation test is considered as positive. Water should be at room temperature. Because, if the temperature is higher or lower, the test could give arise to other forms of PU (cold or heat urticaria) [28]. Bayle et al. reported a case with AU, dermatographism and cholinergic urticaria at the same time [29]. It is possible to induce AU, heat urticaria, cold urticaria and cholinergic urticaria with applying water at different temperatures [30]. So, one should be very careful to differentiate among these conditions.

Management of AU is difficult. Avoidance is almost impossible. The first-line therapy is H1 antihistamines [11]. Long acting newer antihistamines with fewer side effects are usually preferred. H2 receptors are thought to be not operating in the pathogenesis of PU. Yet there is a case report that claims that H2 antihistamines reduce wheal response [31].

Topical barrier therapies show promising results in AU. They are also safer. Application of oil-in-water emulsions before bathing can reduce wheals. Such physical barriers must be used in the pediatric patients before everything else to prevent the potential side effects of the antihistamines [29].

Phototherapy, both PUVA and narrow-band UVB, has been reported to be effective in AU treatment. Possible action of mechanism is the reduction of mast cell activity and thickening of the skin, mostly epidermis, leading to decreased water penetration [32].

Stanozolol which is used in the treatment of hereditary angioedema was shown to be effective in one male patient at a dose of 10 mg daily [25].

4. Contact urticaria

Contact urticaria is the transient whealing and flare of the skin after contact with certain agents. The lesions appear within 60 min of contact and mostly resolve in 2–24 h [33]. Contact urticaria can be both immunological (IgE mediated) or non-immunological. Mostly, non-immunological mechanisms are seen. It can be provoked in all persons without the need of prior sensitization [34].

The lesions in contact urticaria appear as a result of the release of vasoactive amines such as histamine, leukotrienes, substance P and prostaglandins, independent from immunological processes. The lesions are localized to the contact area causing no systemic symptoms. The causative contact agents can be insects, metals, alcohol, balsam of Peru, sodium benzoate, sorbic acid, fruits, vegetables, jellyfish, sea anemones and corals [33–35].

Contact urticaria is rarely due to immunological causes, that is, allergic. In this case, it is caused by antigen-antibody type 1 IgE-mediated hypersensitivity reaction. The contact antigen penetrates the skin and binds with specific IgE antibodies on dermal mast cells. Histamine and some other mediators such as kinin and prostaglandins are released. As a result, erythema and hives are observed [35]. Sometimes systemic symptoms (rhinitis, conjunctivitis and

asthma) can accompany the cutaneous manifestations [36]. The triggering agent in contact urticaria can be rubber latex, antibiotics (cephalosporins and streptomycin), foods (potato, fish and apple), cosmetics (hair bleaching products and paraphenylenediamine) and chemicals (isocyanates, chlorhexidine and aluminum) [35].

The mainstay of the therapy is mainly avoidance in contact urticaria [7]. Barrier creams are being used recently with good results [37]. H1 antihistamines make the first line therapy. In case of failure, dose increment, leukotriene antagonists, cyclosporine, omalizumab can be used with variable success rates [34, 35, 37].

5. Conclusion

As a result, we should keep in mind that chronic urticaria is hard to manage. The treatment should be individualized most of the time because of the fact that one patient can respond well to a specific treatment but another patient cannot. Another fact, to remember, is to differentiate cholinergic urticaria from exercise-induced anaphylaxis. Because they are similar entities, but they have different therapy options and courses.

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